Zagazig J. Pharm. Sci., June, 2011 ISSN 1110-5089
Vol. 20, No. 1, pp, 1-8

EFFECT OF DIFFERENT NON IONIC SURFACTANTS ON THE IN-VITRO RELEASE RATE OF A NON STEROIDAL ANTI-INFLAMMATORY DRUG FROM SOME LIPOPHILIC SUPPOSITORY BASES

Sayed H. Auda*, Mahmoud M. Ahmed, S. Abd El-Rasoul
Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut branch, Assiut, Egypt.

ABSTRACT

Formulation of tolmetin sodium suppositories was carried out using different lipophilic bases as Novatta, suppocir NA10, suppocir W35, suppocir AM, Witepsol E75 and Witepsol H15. The in vitro release study of 200 mg tolmetin sodium suppository from these bases was performed in Sorensen's phosphate buffer (pH 7.4) at 37 °C. The results obtained revealed that Novatta and suppocir W35 gave the highest release rate followed by suppocir NA10, Witesol E75, Witepsol H15 and Suppocir AM respectively. The effect of type and concentrations of different non ionic surfactants as polysorbate 20, polysorbate 60, polysorbate 80, Brij 35, Brij 58, Myrj 53 and Myrj 59 on the drug release from suppocir AM was investigated.

INTRODUCTION

Tolmetin is a pyrrole, acetic acid derivative, non-steroidal anti-inflammatory drug commonly used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and periarticular disorders. It inhibits cyclooxygenase activity with a reduction in the tissue production of prostaglandins.[1,2]

Suppositories have been recognized as an alternative to the oral route in situation as when the patient is comatose, unable to swallow or when the drug produces nausea or vomiting. In the light of this, efforts have been made in recent times to present a good number of drugs in suppository form.[3-5] The aim of this study to evaluate some lipophilic suppository bases in order to determine bases capable of ensuring a rapid release of tolmetin sodium. Possiblity of improvement of the drug release by incorporation of different non ionic surfactants was also investigated. Also the kinetic study of the in vitro release of tolmetin from lipophilic suppository bases was determined.

EXPERIMENTAL

Materials

Tolmetin was kindly provided by MInapharm Co. for pharmaceuticals (10th Ramadan, Cairo, Egypt).suppocir AM, NA10, W35 and Novata (Gattefosse, Establishment, France). Witepsol H15 and E 75 (Dynamit, Nobil, Germany). Methanol, polysorbate (Tween) 20, 60 and 80 (El-Nasr-Pharm. Chem. Co., Cairo, Egypt). Brij 35 and 58 [Atlas Chem. Ind., USA]. Myrj 53and 59 (Sigma, USA). All other chemicals and solvents were of analytical grade.

Equipment

Dissolution Apparatus SR6 Dissolution Test I station (Hanson Research Corporation, Chats worth California, USA).Double beam UV spectrophotometer (Shimadzu Corpoaration, Japan).Erweka hardness tester (Model SBT, Germany). Electrothermal melting point apparatus (Gallenkamp, England).Centrifuge (Xian He, model 800, China).

Methods

Preparation of tolmetin sodium suppositories.

Lipophilic suppository bases containing 200 mg of the drug were prepared by using the melting technique[6], where the used bases were melted over a water bath, the drug added subsequently with stirring after each addition untill homogenous mass was produced and poured into moulds and allowed to cool. The formed suppositories were removed from the mould. Drug displacement values in the used bases were determined and the amount of tolmetin sodium per suppository was calculated. Also suppositories having an additional 2,4,6% w/w of polysorbate 20, polysorbate 60, polysorbate 80, Brij 35, Brij 58 , Myrj 53 and Myrj 59 were prepared using suppocir AM.[7]

Drug content uniformity of the prepared suppositories:

The test was performed to examine the efficiency of the method of preparation. Ten randomly selected suppositories from each batch were assayed individually. A preweighed suppository was placed in 900 ml of phosphate buffer of pH 7.4 which then heated to 50 °C with occasional stirring and allowed to cool. A filtered sample was withdrawn, suitably diluted and assayed spectrophotometrically for drug content at 324 nm.

Hardness test for the prepared suppositories.

Formulated suppositories were tested for hardness using the Erweka hardness tester at 25 °C

Determination of the softening (disintegration) time for suppositories.

The test was preformed according to BP 1998 procedure. The time in minutes required for complete disintegration of the suppository was recorded as the disintegration time.[8]

Determination of the melting point.

Melting point of the prepared suppositories was determined using open capillary tubes and Gallenkamp melting point apparatus.

In vitro release of tolmetin sodium from the prepared suppository bases.

The in vitro release of tolmetin sodium from suppositories was examined by using the USP rotating basket dissolution apparatus. Each suppository was placed in a basket immersed in a flask containing 500 ml of Sorensen's phosphate buffer (pH 7.4). The basket was rotated at 60 rpm at a constant temperature of 37 ± 0.5 °C. At predetermined time intervals 2 ml samples were withdrawn. To compensate for sampling, 2 ml of fresh buffer was added to the dissolution flask. The absorbance of this solution was spectrophotometrically measured at 324 nm using phosphate buffer as a blank, and the drug concentration was subsequently calculated. Each experiment was carried out in duplicate.[9,10] Also the in vitro release of Supocir AM containing different contractions of non ionic surfactants was investigated.[11]

Results and Discussion

Quality control tests of the prepared suppositories:

All the prepared suppositories passed the quality control tests. Incorporation of tolmetin sodium in different bases had a little or no effect on the physical characters namely hardness, melting point and softening time of the plain bases.

Drug content uniformity:

The drug content was found to be 98 – 103%, which means a good agreement with the pharmacopeial standards.

Hardness:

The prepared suppositories exhibited a reasonable degree of hardness ranging between 2.25 and 4.75 kg which allow the prepared suppositories to be handled without breakage. The results are listed in table (1).

Softening (disintegration) time:

Softening or disintegration time was determined.[3] The different formulations exhibited different disintegration times. They are either dissolved or softened and melted within the range of 18 min., for fatty bases. Rapid disintegration would allow fast release of the drug from the prepared suppositories. The results are listed in table (1).

Melting point:

The melting points for suppositories containing the drug determined by open capillary method are listed in Table (1).

Table (1): Physical characterization of the prepared suppositories.

Medicated suppositories containing the following bases	Melting point (°C)	Hardness (kg)	Softening time (min.)
Novatta	33.5	2.40	9
Suppocir NA10	35.5	2.75	10
Suppocir W35	35.0	3.00	8
Suppocir CM	38.0	4.75	18
Suppocir AM	37.0	4.50	15
Witepsol H15	35.0	2.25	13
Witepsol E75	37.0	3.50	10

***In vitro* release of tolmetin sodium from the prepared suppository bases.**

The release profiles of tolmetin sodium from suppository bases are graphically represented in Figs. (1). The release of tolmetin sodium from fatty bases was in the following order:

Novatta = suppocir W 35 > suppocir NA 10 = Witepsol E 75 > Witepsol H 15 > Suppocir AM > Suppocir CM.

It was noted that, these bases gave the highest drug release relative to the other investigated bases. This observation may be attributed to the fact that tolmetin sodium is a water soluble drug.[12] has a higher affinity towards the hydrophilic bases than the fatty bases. It is clear that the release of drug from novatta and suppocir W35 was the highest because they have low melting point and short softening time. These two parameters are considered to be the rate limiting steps in the release of drug from bases. These results can be attributed to the release rate dependency on both melting behaviour and chemical composition of the used bases. This agreed with Webster *et al.*[13] who proved that the release of amoxycillin from novatta was the highest among the investigated bases.

ISSN 1110-5089

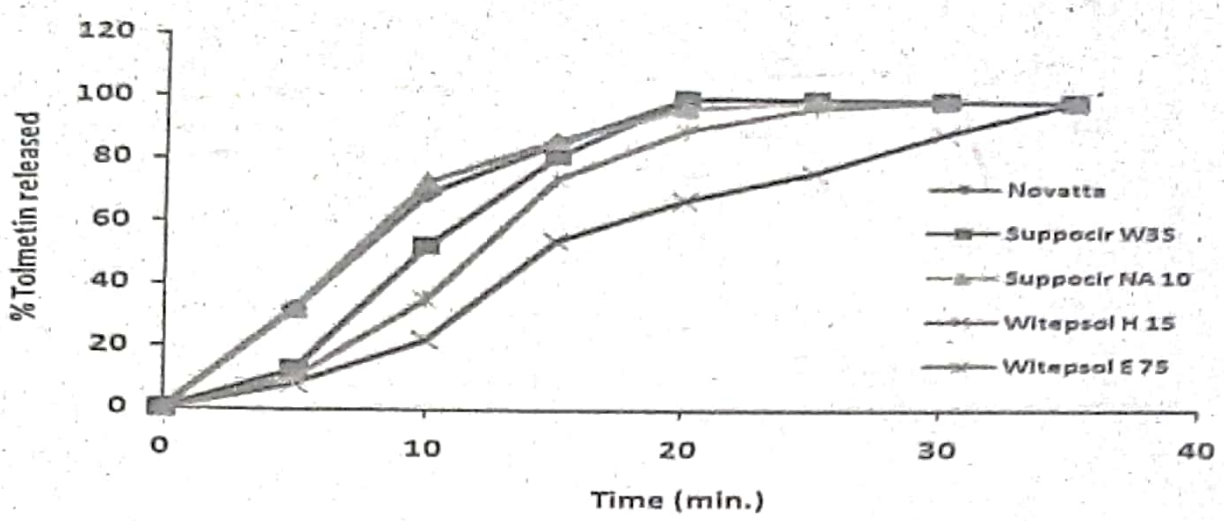

Fig. (1): Release profile of tolmetin sodium from lipophilic suppository bases.

In vitro release study of tolmetin sodium from Suppocir AM containing non ionic surfactants of different ratios.

The release profiles of tolmetin sodium from suppocir AM containing non ionic surfactants (in different concentrations) were studied. The incorporation of surfactants caused an increase or decrease in the amount of drug release depending on the nature and concentration of the surfactant used.

Addition of ester type surfactants [polysorbates] showed an increase in the amount of drug released from suppocir AM when used in optimum concentration as graphically represented by Figs. (2-4. The optimum concentration for polysorbate 20, 60 and 80 is 6%. The enhanced drug release after incorporation of the surfactants may be due to increased wettability and solubilization of the medicament. However further increase in the surfactant concentration above the optimum concentration decreased the drug release, which may be due to the entrapment of the drug inside the micellar core of the surfactant.[14,15] The difference in the release rate of drug could be attributed to the difference in the chemical structure of the surfactants. The tested ester type non ionic surfactants could be arranged according to their efficiency to release tolmetin sodium from suppocir AM as the following: 6% polysorbate 60 > 6% polysorbate 20 > 6% polysorbate 80.

The effect of Brij 35 and 58, Myrj 53 and 59 is graphically represented by Figures (5 - 8). It has been found that increasing the concentration of Brijs and Myrjs leads to a decrease in the amount of drug released so the optimum concentration for both Brijs and Myrjs is 2%. These results are in a good agreement with that obtained by some authors [16], who proved that the release of ketoprofen was increased by the addition of polysorbate 80 and Myrj 53.

Kinetic analysis of the release data.

Kinetic analysis of tolmetin sodium release data was investigated according to zero order, first order.[17] and Higuchi diffusion model.[18] In order to determine the release model which describes the release pattern of the drug, from suppository bases.

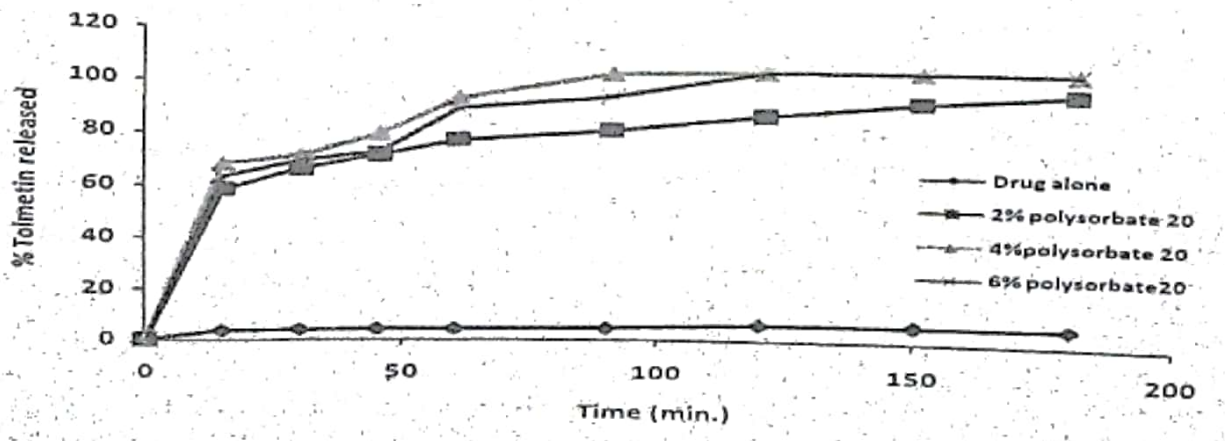

Fig. (2): Effect of polysorbate 20 on the release porofile of tolmetin sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 ^{0}C.

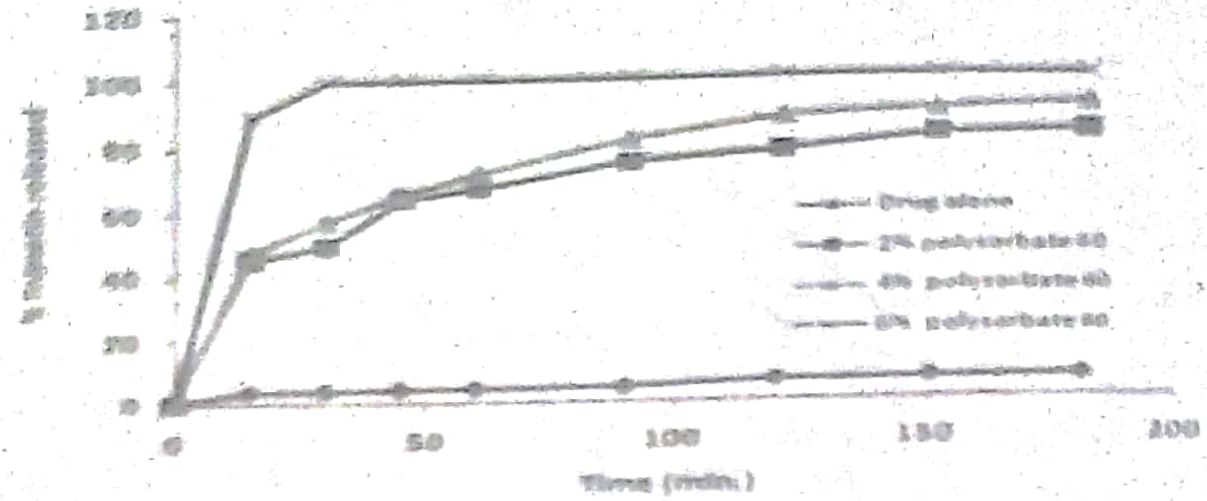

Figure (3): Effect of polysorbate 80 on the release profile of valsartan sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 °C.

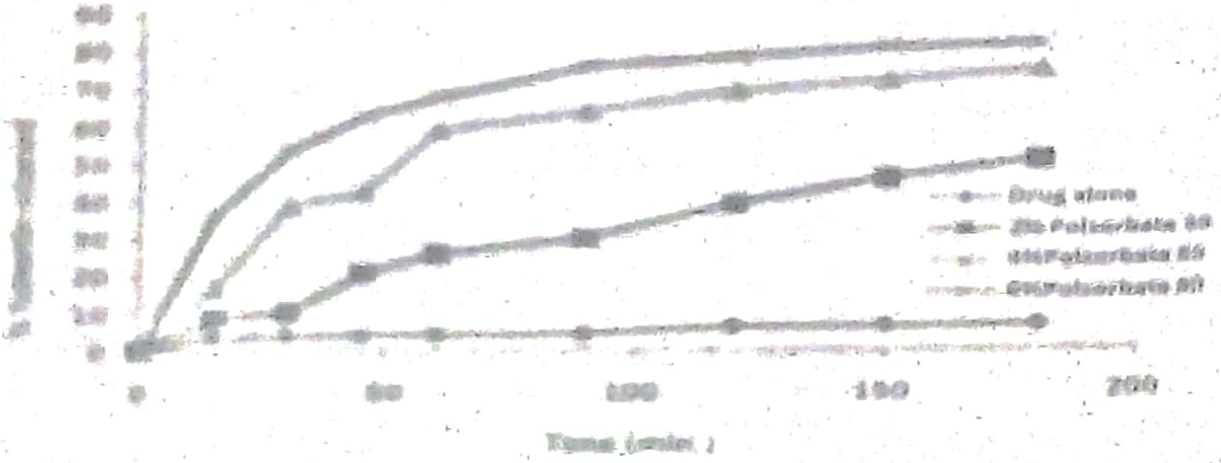

Fig. (4): Effect of polysorbate 80 on the release profile of valsartan sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 °C.

Fig. (5): Effect of time on the release profile of valsartan sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 °C.

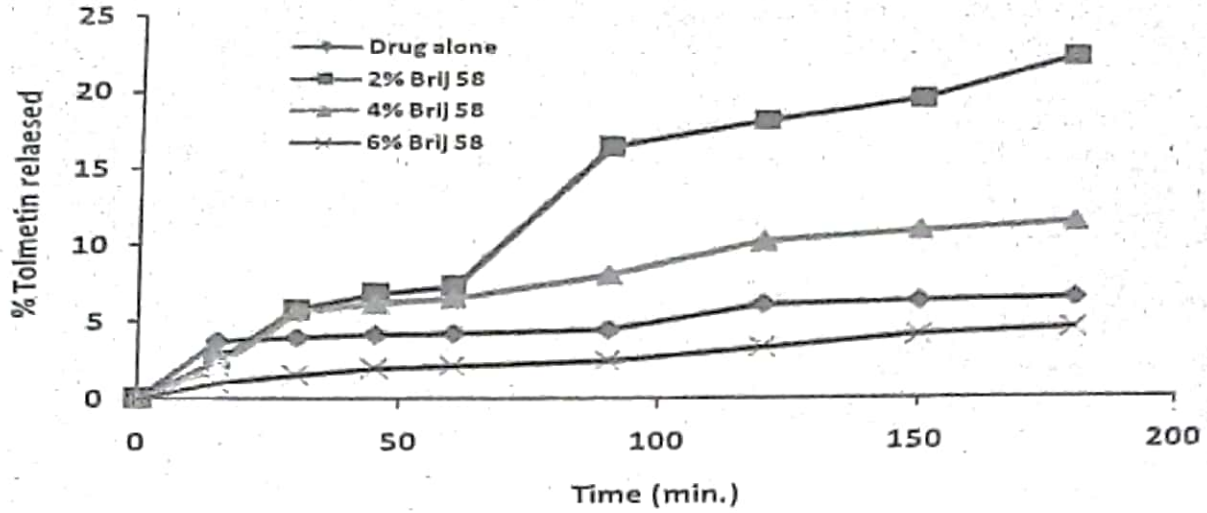

Fig. (6): Effect of Brij 58 on the release porofile of tolmetin sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 ^{0}C.

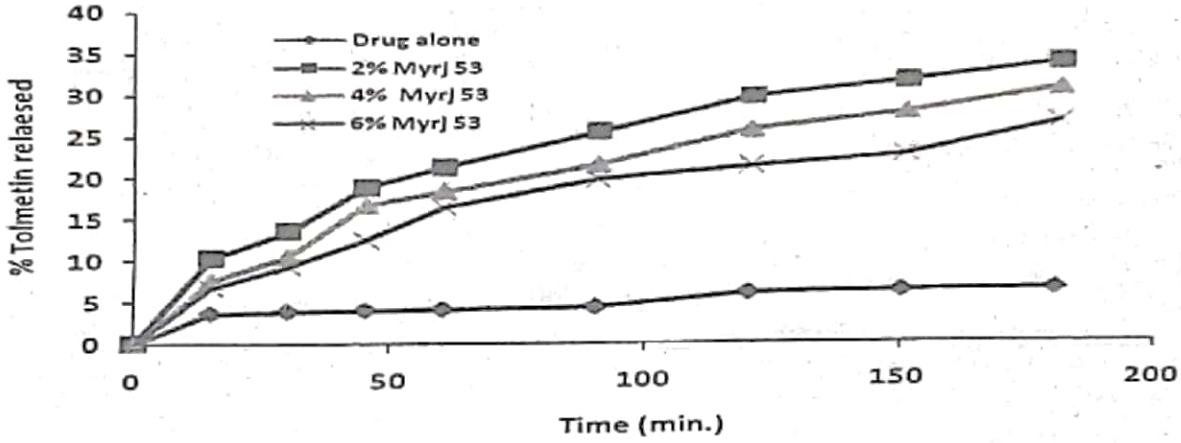

Fig. (7): Effect of Myrj 53 on the release porofile of tolmetin sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 ^{0}C.

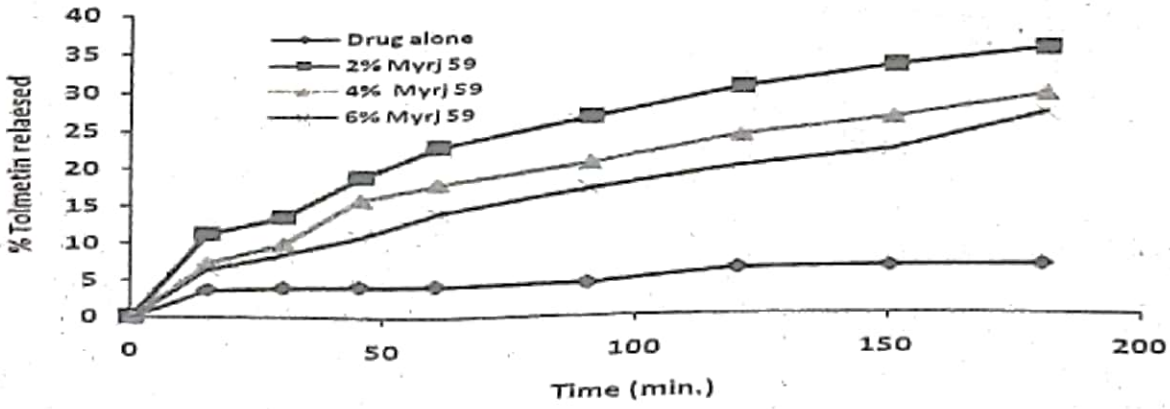

Fig. (8): Effect of Myrj 59 on the release porofile of tolmetin sodium from Suppocir AM in phosphate buffer of pH 7.4 at 37 ^{0}C.

Kinetic assessment of tolmetin *in vitro* release data.

The results showed that the release of tolmetin from lipophilic suppository bases follow diffusion model zero and first order according to the type and nature of suppository base incorporated. Table (2 and 3): shows that the release rates of tolmetin from lipophilic suppository bases follow diffusion model with exception of that obtained from Suppocir NA10 and suppocir AM which followed first and zero order respectively. Suppocir AM with the optimum concentrations of non ionic surfactants, which gives the highest release rate of the drug from these base (6% of polysorbate 20,60 ,80 and 2% of Brij 35.58 and Myrj 53.59) was investigated in table (4 and 5). The results showed that all formulae obeyed diffusion model with exception of that obtained from Suppocir Am with 6% of polysorbate 60 which followed zero order.

Table (2): Kinetic parameters for the in vitro release of tolmetin from lipophilic suppository bases based on zero , first order and Highuchi diffusion model.

Order		Suppository bases					
		Novatta	Suppocir W 35	Suppocir NA 10	Witepsol E 75	Witepsol H 15	Suupocir AM
Zero order	I	16.60	10.93	38.41	2.50	2.01	3.26
	S	4.40	5.80	2.44	3.72	3.07	0.019
	R	0.970	0.986	0.872	0.942	0.980	0.9612
	K	4.40	5.80	2.44	3.72	3.07	0.019
	$t_{(1/2)}$	11.36	8.61	20.41	13.42	16.23	2624.01
First order	I	2.92	3.12	2.47	2.86	2.67	1.98
	S	0.158	0.166	0.103	0.110	0.071	8.7
	R	0.905	0.898	0.992	0.939	0.842	0.9610
	K	0.365	0.383	0.237	0.254	0.164	0.0002
	$t_{(1/2)}$	1.89	1.80	2.91	2.72	4.21	3449.34
Higuchi diffusion	I	31.72	73.61	0.337	52.90	51.26	2.03
	S	30.07	39.35	20.21	29.87	25.74	0.329
	R	0.989	0.997	0.925	0.971	0.991	0.940
	K	30.07	39.35	20.21	29.87	25.74	0.329
	$t_{(1/2)}$	2.76	1.61	6.11	2.80	3.77	23069.9

I= Intercept S = slope R = Correlation coefficient

K = Specific rate constant (min.$^{-1}$) $t_{(1/2)}$ = Half life (min.)

Table (3): Kinetic parameters for the in vitro release of Tolmetin from lipophilic suppository bases according to a suitable order or model.

	Suppository bases					
	Novatta	Suppocir W 35	Suppocir NA 10	Witepsol E 75	Witepsol H 15	Suppocir AM
Intercept	31.72	73.61	2.47	52.90	51.26	3.26
Slope	30.07	39.35	0.103	29.87	25.74	0.019
R	0.989	0.997	0.992	0.971	0.991	0.9612
K	30.07	39.35	0.237	29.87	25.74	0.019
$T_{1/2}$	2.76	1.61	2.91	2.80	3.77	2624.01
Order	Higuchi	Higuchi	First	Higuchi	Higuchi	Zero

Table (4): Kinetic parameters for the in vitro release of tolmetin from Suppocir AM with optimum concentrations of non ionic surfactants based on zero , first order and Highuchi diffusion model.

Order		Suppocir AM with optimum concentrations of surfactants						
		Suppocir AM with 6% polysorbate 20,60 and 80			Suppocir AM with 2% Brij 35, 58 and Myrj 53,5			
		poly 20	Poly 60	Ploy 80	Brij 35	Brij 58	Myrj 53	Myrj 59
Zero order	I	58.57	83.1	47.24	13.29	1.64	11.03	11.30
	S	0.362	0.343	0.224	0.139	0.124	0.140	0.14
	R	0.967	0.921	0.867	0.949	0.971	0.969	0.972
	K	0.362	0.343	0.224	0.139	0.124	0.140	0.14
	$t_{(1/2)}$	137.98	145.63	222.51	358.73	402.68	357.10	348.50
First order	I	2.16	2.41	1.73	1.94	1.994	1.95	1.95
	S	0.019	0.057	0.002	0.0008	0.0006	0.0007	0.008
	R	0.903	0.881	0.930	0.961	0.974	0.978	0.980
	K	0.045	0.132	0.006	0.001	0.0001	0.001	0.001
	$t_{(1/2)}$	15.20	5.24	104.35	370.81	485.01	378.82	366.35
Higuchi diffusion	I	39.81	74.68	29.38	3.13	6.93	0.973	1.06
	S	5.49	3.49	4.26	2.53	2.20	2.53	2.58
	R	0.973	0.889	0.932	0.979	0.978	0.993	0.993
	K	5.49	3.49	4.26	2.53	2.20	2.53	2.58
	$t_{(1/2)}$	82.85	204.48	137.64	387.89	513.12	389.69	373.52

Table (5): Kinetic parameters for the in vitro release of tolmetin from Suppocir AM with optimum concentrations of non ionic surfactants according to a suitable order or model.

	Suppocir AM with optimum concentrations of surfactants						
	Suppocir AM with 6% polysorbates 20,60 and 80			Suppocir AM with 2% Brij 35, 58 and Myrj 53,59			
	poly 20	Poly 60	Ploy 80	Brij 35	Brij 58	Myrj 53	Myrj 59
Intercept	39.81	83.1	29.38	3.13	6.93	0.973	1.06
Slope	5.49	0.343	4.26	2.53	2.20	2.53	2.58
R	0.973	0.921	0.932	0.979	0.978	0.993	0.993
K	5.49	0.343	4.26	2.53	2.20	2.53	2.58
$T_{1/2}$	82.85	145.63	137.64	387.89	513.12	389.69	373.52
Order	Higuchi	Zero	Higuchi	Higuchi	Higuchi	Higuchi	Higuchi

REFERENCES

1. Lindsley D., Carol B., **Clinical Pediatric**, 29, 10, (1999).
2. Katzung B.G. **Basic and clinical pharmacology.** 9th ed. New York: McGraw Hill, (2004).
3. Adegboye T.A., Itiola O.A., **Afr. J. Med. Med. Sci.**, 32, 247, (2003).
4. Taha T.I., Zaghloul A.A., Samy A.M., Al-Saidan S., Kassem A.A., Khan M.A., **Int. J. Pharm.**, 297, 3 (2004).
5. Pasztor E., Csoka G., Klebvoich I., Antal I., **Eur. J. Pharm. Sci.**, 6, 34, (2007).
6. Collett D.M., Aulton M.E., **"Pharmacentical Practice"** Longman Group UK Ltd., 135 (1990).
7. Abd El - Hady S.S., Mortada N., Awad G.A.S., Zaki N.M., Taha R. A., **Egypt. J., Biomed.Sci.**, 7, 72 (2001).
8. **British pharmacopiae,** London, Her Majesty's stationary office (1998).
9. Iwata M., Takayama k., Tahahashi Y., Obata Y., Shirotake S. et al., **J. Hosp. Pharma.**, 24, 357, (1998).
10. Zia Amirhosseini P., Ojingwa J.C., Spahn Langguth H., McDonagh A.F., Benet L.Z. **Clin. Pharmcol.Ther.**, 55, 21, (1994).
11. Oladimeji F.A., Omaruyi S.I.and Onyeji C.O. **Afr. J.Biotech.**, 5, 1775, (2006).
12. Martindale W., **The Extrapharmacopoeia**, 32th Ed., Reynold, J.E.F. Ed., The Pharmaceutical Press, London, p. 12, (2000).
13. Webster J.A., Dowse R., Walker R.B. **Drug Dev. Ind. Pharm.**, 24, 35, (1998):.
14. El-Assasy A., Soliman I.I., Farid S.S. **Bull. Fac. Pharm., Cairo Univ.**, 35 151, (1997).
15. Abdel Bary A., Mohamoud H.A., Naim O. **Bull. Fac. Pharm. Cairo Univ.**, 1, 51, (1995).
16. Ramadan E.M., Mans., **J. Pharm. Sci.**, 6, 82, (1990).
17. Martin A., Swarbrick J., Cammarta A., **Physical Pharmacy**, 4th Ed. Lea and Febiger Phil., 584, 358, 403, (1993).
18. Higuchi W.I., **Pharm. sci.**, 51,802, (1962).

Received: 3/01/2011
Accepted: 14/3/2011

تأثير منشطات السطح غير الأيونية علي الإنطلاق الدوائي لأحد مضادات الإلتهاب غير الإستيرويدية من بعض قواعد الأقماع المحبة للدهون

سيد عودة و محمود محمد أحمد وصالح عبد الرسول
قسم الصيدلانيات و الصيدلة الصناعية- جامعة الأزهر-أسيوط

تم في هذه الدراسة صياغة عقار التولمتين صوديوم من قواعد الأقماع الدهنية المصنعة مثل سوبوسير ن أ ، سوبوسير س م، سوبوسير هـ٣٥، سوبوسير أ م ، نوفاتا ، ويتبسول هـ ١٥ ويتبسول ى ٧٥ . و تم تحضير أقماع شرجية ذات وزن ٢ جرام ، تحتوى على ٢٠٠ ملجرام دواء منفرداً، تم دراسة الخواص الفيزيقية للأقماع الشرجية المحضرة مثل نسبة الاختلاف الوزنى للأقماع ، التقدير الكمى للجرعة ، درجة الصلابة ودرجة الانصهار ، وقد وجد أن الخواص الفيزيقية للأقماع المحضرة تتلائم مع القيم المسجلة لدستور الأدوية البريطانى لعام ١٩٩٨م . تم دراسة الانطلاق المعملى للعقار فى محلول الفوسفات المنظم عند الأس الأيدروجينى ٧.٤ والذى يماثل الأس الأيدروجينى للعصارة المعوية فى الإنسان. وقد أثبتت النتائج أن الصياغة المحتوية على سوبوسير هـ ٣٥ ونوفاتا تعطى أعلى وأسرع معدل انطلاق للعقار . تم إدماج مواد ذات نشاط سطحى غير متأينة محبة للماء مثل مجموعات توين ، بريج ومريج لدراسة مدى تأثيرها على انطلاق العقار من الأقماع الشرجية المحضرة من قاعدة سوبوسير أ . م والتى تحتوى على العقار .
وقد لوحظ أن استخدام هذه المجموعات قد أدى إلى زيادة معدل ذوبان أو انطلاق العقار، وكلما زاد تركيز التوين زاد معدل انطلاق الدواء وقد أوضحت النتائج أن مجموعة المريج والبريج قد أدت إلى زيادة انطلاق العقار فقط فى التركيز المنخفض (٢%). وأنه كلما زاد تركيز المريج والبريج كلما قل معدل انطلاق العقار ، وذلك لقلة كمية الدواء الحر القابل للانطلاق عند استخدام تركيزات عالية.
كما تم أيضا تعيين حركية انطلاق العقار من الأقماع الشرجية المحضره من القواعد الدهنية وقاعدة سبوسير أ م التي تحتوي علي تركيزات محدده من المواد ذات النشاط السطحي الغير متأينة باستخدام نماذج حركية مختلفة.